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Review Article

Emerging roles of cuproptosis in liver diseases

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ABSTRACT

Intracellular copper levels should be maintained within a controlled range to obtain copper homeostasis. Cuproptosis, a newly discovered form of cell death, occurs when excessive copper ions bind to the lipoylated enzymes in the tricarboxylic acid cycle, which leads to lipoylated protein aggregation, proteotoxic stress, and ultimately cell death. Herein, we summarize the current knowledge regarding copper metabolism, the discovery and molecular mechanism of cuproptosis. In addition, we discuss the implications of cuproptosis in the pathogenesis of various liver diseases, including hepatocellular carcinoma (HCC), Wilson disease (WD), metabolic-associated fatty liver disease (MAFLD), liver fibrosis, hepatic ischemia-reperfusion injury (HIRI) and drug-induced liver injury (DILI). Understanding the mechanism of cuproptosis can not only provide deeper insights into the pathogenesis of liver diseases but also open up new avenues for the development of targeted therapies.

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1. Introduction

Copper is an essential trace element for human body, it participates in a variety of physiological processes, such as cell respiration and antioxidant defense. Moreover, as a cofactor of numerous fundamental biological enzymes such as superoxide dismutase and cytochrome C oxidase, copper is involved in regulating diverse physiological processes such as cell metabolism, cell growth and signal transduction [1]. Remarkably, the content of copper should be maintained in a narrow range under normal circumstances. And the abnormal changes in intracellular copper content may lead to toxic effects related to copper ions [2], which results in cell damage and ultimately contributes to the development of various diseases. Therefore, the maintenance of copper homeostasis is pivotal for human health. Cuproptosis is a newly identified form of cell death, it is triggered by the imbalances in copper homeostasis. Cuproptosis exhibits characteristics that are entirely different from other known cell death modes such as apoptosis, autophagy, pyroptosis and ferroptosis. During the cuproptosis process, copper ions can bind to the lipoylated enzymes in the tricarboxylic acid (TCA) cycle, which leads to the aggregation of lipoylated proteins and the down-regulation of Fe-S cluster protein expression, and ultimately initiates cell death [3].

As the largest digestive organ of human body, the liver performs critical physiological functions including metabolism, detoxification, synthesis, and so on. Liver diseases encompass a spectrum of conditions such as viral hepatitis, alcoholic liver disease, metabolic-associated fatty liver disease (MAFLD), liver fibrosis, cirrhosis, and liver cancer, etc. [4]. In the development and progression of these diseases, cuproptosis is anticipated to emerge as a significant pathological mechanism. Therefore, this paper reviews the metabolism of copper, the underlying molecular mechanisms of cuproptosis, and the emerging roles of cuproptosis in multiple liver diseases. It will provide novel insights into the treatment of liver-related disorders.

2. Cuproptosis

2.1. Copper and copper metabolism in the human body

Copper, as one of the essential trace elements in human body, has a variety of biological functions. It possesses strong REDOX activity and protein binding ability, which means it can be used as a cofactor of various essential enzymes and participate in multiple biological processes [1]. Especially, Cu plays a predominant role in mitochondrial electron transfer chain (mtETC) and TCA cycle as an

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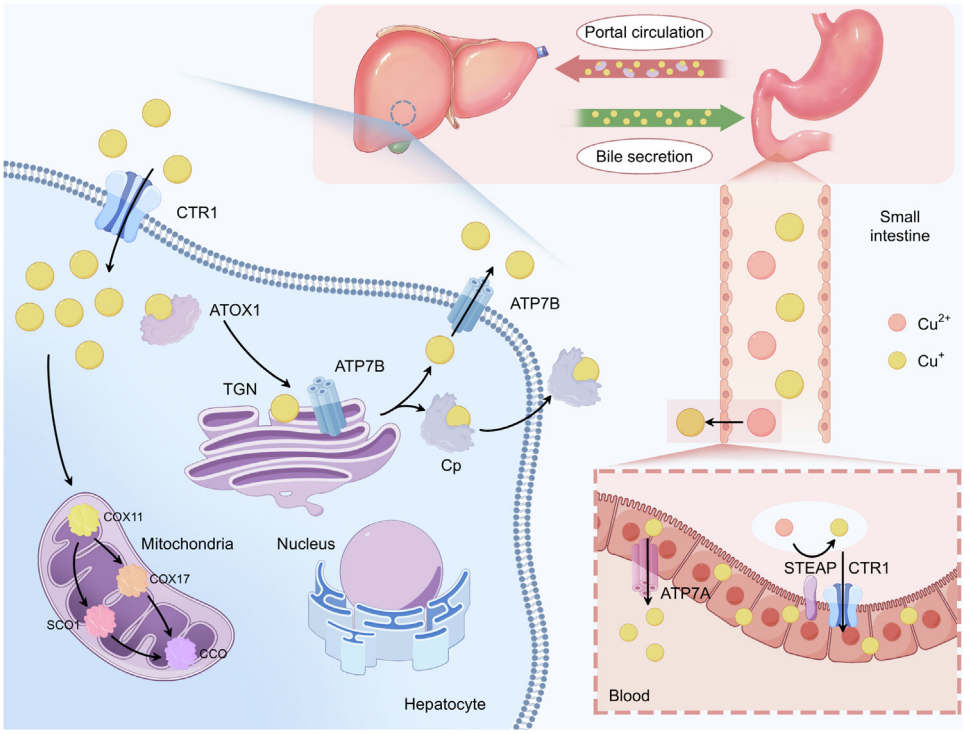

Fig. 1. Copper Metabolism in the Human Body. Cu^{2+} from food enters the small intestine, where it is reduced to Cu^{+} by the enzyme STEAP on the surface of intestinal epithelial cells. The reduced Cu^{+} is then transported into the epithelial cells by CTR1 and subsequently transferred into the bloodstream by ATP7A, eventually reaching the liver. In the liver, a portion of Cu^{+} is incorporated into ceruloplasmin, and then released back into the bloodstream to be distributed throughout the body. The remaining Cu^{+} is transported by ATP7B into the gallbladder, where it is excreted into the small intestine with bile for reabsorption or discharge.

essential element required for mitochondrial oxidative phosphorylation and ATP production [5].

Copper is mainly ingested from diet in the form of Cu^{2+} [6]. Cu^{2+} cannot be taken up directly by cells until it is reduced to Cu^{+} by metalloreductase six-transmembrane epithelial antigen of the prostate (STEAP). And Cu^{+} uptake is mediated by solute carrier family 31 member 1 (SLC31A1), also known as copper transporter 1 (CTR1) [7]. Once entering the circulation, copper is transported to organs and tissues through the body by binding to plasma proteins such as ceruloplasmin (Cp), albumin, and so on. Liver is the main storage organ of copper ions in the human body. In the hepatocytes, copper is shuttled to various cellular components including the cytoplasm, mitochondria, Golgi apparatus and nucleus for further cellular metabolic processes. And the trafficking of intracellular copper is tightly regulated by a sophisticated system of high-affinity copper chaperones, such as copper chaperone for superoxide dismutase (CCS), cytochrome c oxidase (COX) and antioxidant 1 copper chaperone (ATOX1) [8]. ATOX1 transfers Cu^{+} from the trans-Golgi network (TGN) to copper transporters ATP7A and ATP7B, which are crucial for copper export from cells. When intracellular copper levels are higher than the normal limit, these transporters undergo a conformational change and translocate from the TGNs to the cell membrane, where they pump copper ions into the extracellular space [9]. Then copper is discharged into the small intestine with bile, where it is reabsorbed or excreted [10] (Fig. 1). Therefore, copper content can be dynamically kept within a controllable range through proper absorption and discharge of copper, known as copper homeostasis, which plays an indispensable role in maintaining normal human physiological activities [11]. And the imbalance of copper homeostasis can seriously harm human health. When the excess accumulation of copper in the body exceeds the threshold, it can evoke cytotoxicity and cell death [5].

2.2. Discovery and molecular mechanism of cuproptosis

Before the term ‘cuproptosis’ was coined, various modes of cell death including apoptosis, necroptosis, pyroptosis, autophagy, and ferroptosis had already been discovered. Apoptosis is a biological process through which cells undergo an orderly and controlled death [12]. This process holds a pivotal place in maintaining cellular homeostasis, development, and tissue remodeling. The typical features of apoptosis include cell shrinkage, chromatin condensation, membrane blebbing, and the formation of apoptotic bodies. Apoptosis can be triggered through two main pathways: intrinsic pathway and extrinsic pathway. The former is activated by internal signals, such as DNA damage, oxidative stress or other cellular stresses. It involves the mitochondria and the release of cytochrome c, which activates caspase-9. The latter is triggered by external signals, such as the binding of death ligands to their receptors on the cell surface, leading to the activation of caspase-8 [13,14]. Of note, this process typically does not evoke inflammatory responses. Unlike apoptosis, pyroptosis is a form of programmed cell death that is characterized by its inflammatory nature. It is primarily mediated by specific caspases, particularly caspase-1 or Caspase-4/5/11, which is activated in response to various stimuli, including pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Pyroptosis often involves the formation and activation of inflammasomes, which facilitates the cleavage of pro-caspase-1 into its active form and ensuing processing and maturation of pro-inflammatory cytokines, such as interleukin-1β and interleukin-18. Pyroptosiss is characterized by cell swelling, membrane rupture, and Gasdemin-mediated pore formation [15]. This rupture leads to the release of cellular contents into the extracellular space, which triggers an inflammatory response and recruits immune cells [16–18]. Pyroptosis often serves as a defense mechanism against infections by promoting in-

flammation and helping to eliminate pathogens. However, excessive pyroptosis can lead to tissue damage and has been linked to various diseases, including infectious diseases, autoimmune disorders and neurodegenerative diseases. The term autophagy means 'self-eating', is a cellular process that involves the degradation and recycling of cellular components. Double-membrane structures called autophagosomes form, and engulf damaged organelles, misfolded proteins, or other cellular debris. Then the autophagosomes fuse with lysosomes, where the contents are degraded by lysosomal enzymes. And the resultant macromolecules (amino acids, fatty acids, and so on) are released back into the cytoplasm for reuse in cellular metabolism [19,20]. Autophagy is a vital cellular process that plays a pivotal role in maintaining cellular homeostasis, promoting cellular adaptation to stress conditions (starvation, hypoxia and oxidative stress), and regulating immune responses. Autophagy-related proteins (ATGs) are a group of proteins that play crucial roles in the regulation and execution of the autophagy process. They are involved in various stages of autophagy, including the initiation, formation of autophagosomes, fusion with lysosomes, and degradation of cellular components. Dysregulation of ATGs can lead to various diseases, including neurodegenerative disorders, metabolic disorders, and cancer [21]. Ferroptosis is a unique regulated cell death, and characterized by iron-dependent lipid peroxidation and oxidative stress [22]. Lipid peroxides are formed when polyunsaturated fatty acids in cell membranes undergo oxidative damage catalyzed by reactive oxygen species (ROS). Ferroptosis is heavily reliant on iron, because it can catalyze the formation of ROS through Fenton reactions, leading to oxidative damage and promoting ferroptosis. As a critical antioxidant, glutathione (GSH) protects cells from oxidative stress. Glutathione peroxidase 4 (GPX4) is an enzyme that reduces lipid peroxides to non-toxic agents [23,24]. Inhibition or depletion of GPX4 leads to the accumulation of lipid peroxides and triggers ferroptosis. In recent years, ferroptosis has garnered significant interest due to its implications in various physiological and pathological processes.

The term 'cuproptosis' was first introduced in a study published in 2022 by Tsvetkov et al. from Broad Institute of Harvard and MIT. The discovery of cuproptosis marked a significant milestone in the understanding of regulated cell death, which represents a significant advancement in the field of cell biology and highlights the role of copper as a regulator of cell death. Although this novel and unique form of cell death is identified in 2022, the toxic effects of excessive copper accumulation on cells have been recognized for decades [25], particularly in the context of certain diseases like Wilson's disease, where copper buildup leads to cellular damage and death. Nevertheless, the exact mechanism by which copper ions cause cell death has not been clearly defined yet, although several hypotheses have been proposed, including apoptosis, caspase-independent cell death, the induction of ROS, and inhibition of ubiquitin-proteasome system, etc. [3,11,26,27]. These observations pave the way for the later identification of cuproptosis as a distinct form of regulated cell death.

Copper ionophores are compounds that facilitate the transport of copper ions across cellular membranes. They assist in elevating intracellular copper levels by promoting the uptake of copper from the extracellular environment. Therefore, copper ionophores such as elesclomol (ES) are considered as the useful tools to study copper toxicity. Multiple lines of evidence support that cell death induced by copper ionophores (such as ES) primarily depends on the accumulation of copper within cells, rather than the ionophores themselves [3]. To determine the nature of copper-induced cell death, the authors conducted intervention experiments through Caspase 3 activation or BAX/BAK1 knockout, and ruled out the possibility of apoptosis. Similarly, inhibitors targeting other programmed cell death pathways, such as the ferroptosis inhibitor Fer-1 and the necroptosis inhibitor Nec-1, also could not rescue Cu/ES-induced cell death, thus excluded the likelihood of these cell death modes. Consequently, Cu/ES-induced cell death is a novel form of cell death, distinct from all known cell death modes. And the authors named it 'cuproptosis' [3].

Next, the authors demonstrated that cuproptosis is closely linked to mitochondrial function [11]. Cells that depend on mitochondrial respiration exhibit an extremely high sensitivity to copper carriers, nearly 1000 times more than cells relying on glycolysis [3]. Notably, the mitochondrial uncoupler has no effect on copper toxicity, suggesting that mitochondrial respiration, but not ATP production, is required for copper-induced cell death. Subsequently, they documented that FDX1 and protein lipoylation are the key regulators of copper ionophore-induced cell death, since knockout of either FDX1 or lipoylation-related enzymes rescues cells from copper toxicity. FDX1, or ferredoxin 1, encodes a reductase known to reduce Cu^{2+} to its more toxic form, Cu^{1+}, and has been proved to be a direct target of ES. Protein lipoylation is a highly conserved post-translational modification, which involves the attachment of lipoic acid, a confactor that plays a crucial role in mitochondrial metabolism, to specific lysine residues on target proteins. This modification is known to occur on only four enzymes in TCA cycle, including dihydrolipoamide S-acetyltransferase (DLAT) (a subunit of the pyruvate dehydrogenase complex), dihydrolipoamide S-succinyltransferase (DLST), glycine cleavage system protein H (GCSH), and dihydrolipoamide branched chain transacylase E2 (DBT). These lipoylated enzymes exist in mitochondria, and can regulate carbon entry points to the TCA cycle [3,28]. Remarkably, FDX1 and lipoyl synthase (LIAS) were identified as key regulators for copper toxicity using a genome-wide CRISPR screen, since genetic knockout of either FDX1 or LIAS reduces protein lipoylation and inhibits copper-induced cell death [3].

Mechanistically, copper directly binds to TCA cycle proteins, for example, DLAT and DLST, and the lipoylation is required for the binding between them. And copper binding to lipoylated proteins results in lipoylation-dependent oligomerization of DLAT, which is disulfide-bond dependent. Importantly, copper-induced cell death has also been linked to the disruption of iron-sulfur (Fe-S)-containing enzymes. Fe-S proteins are essential cofactors for enzymes involved in the electron transport chain and other biochemical processes. Copper has been shown to block Fe-S cluster formation by inhibiting the activity of relevant mitochondrial assembly proteins. In addition, the aggregation of mitochondrial enzymes may disrupt the function of these Fe-S clusters [11,29]. Together, lipoylated protein aggregation and subsequent Fe-S cluster protein loss lead to proteotoxic stress and ultimately cell death.

Collectively, the molecular mechanism of cuproptosis can be summarized as follows: Cu^{+} not only directly binds to the sulfur moiety in the TCA cycle and leads to the aggregation of lipoylated proteins, but also directly downregulates the expression of Fe-S cluster proteins, ultimately inducing proteotoxic stress and resulting in cell death (Fig. 2).

3. Cuproptosis and liver-related diseases

The discovery of cuproptosis has important implications for understanding diseases associated with copper dysregulation. It highlights the need for maintaining copper homeostasis in cells, since excessive copper accumulation can lead to detrimental effects. Following the initial discovery, ongoing research is focused on elucidating the detailed mechanisms of cuproptosis and exploring its potential therapeutic applications in liver diseases.

3.1. Cuproptosis and liver cancer

Hepatocellular carcinoma (HCC) is the predominant type of primary liver cancer and the fourth leading cause of cancer-related

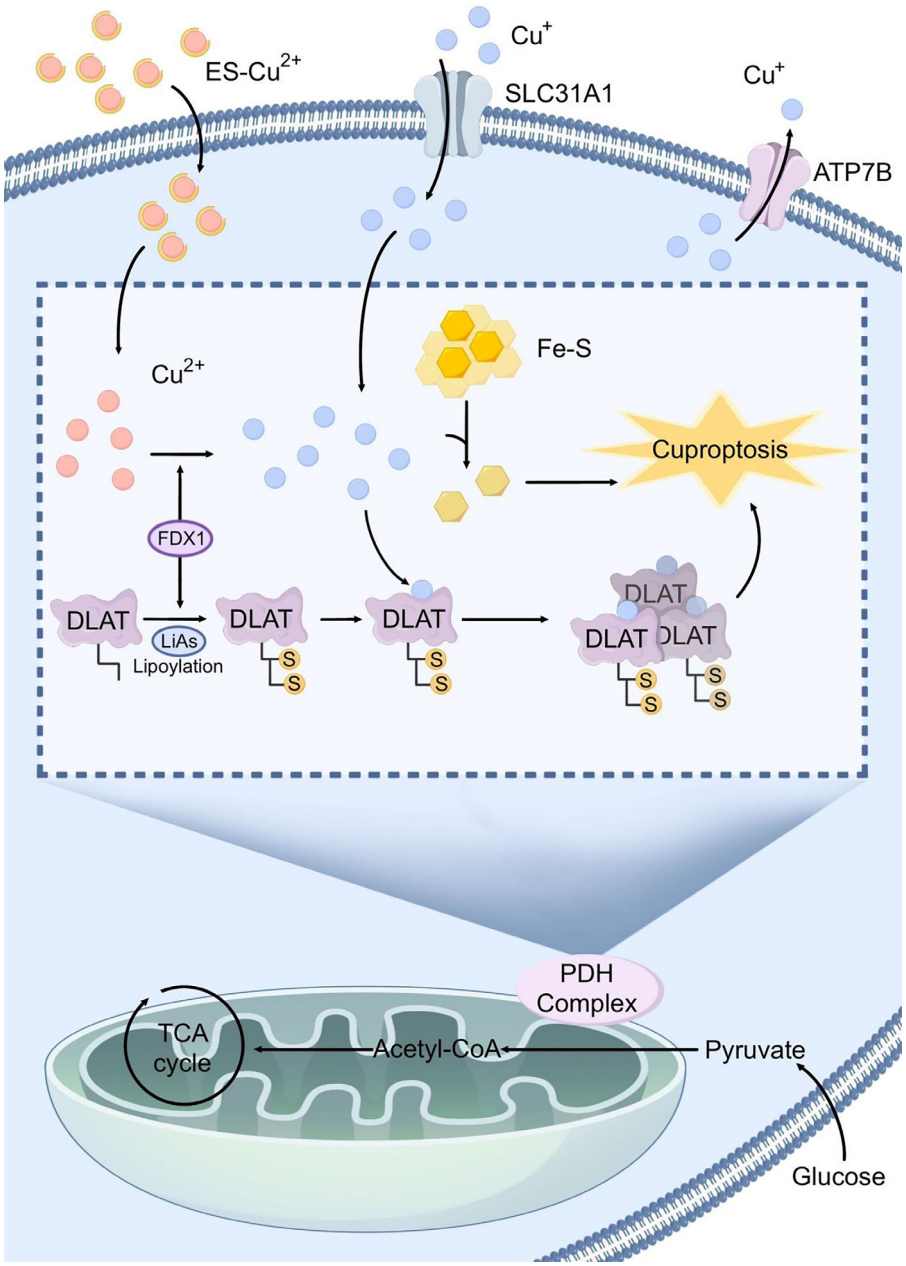

Fig. 2. Molecular Mechanism of Cuproptosis. ES facilitates the transport of Cu^{2+} into mitochondria, while SLC31A1 and ATP7B mediate the uptake and efflux of Cu^{+}, respectively. DLAT, a constituent of the Pyruvate Dehydrogenase (PDH) complex, undergoes lipoylation regulated by FDX1 and LiAS. FDX1 also catalyzes the reduction of Cu^{2+} to Cu^{+}. Cu^{+} not only directly interacts with lipoylated DLAT and leads to its aberrant accumulation and aggregation, but also directly suppresses the expression of Fe-S cluster proteins, ultimately inducing protein toxicity stress and culminating in cell death.

mortality. It is a multistage disorder with a poor prognosis. So far, the pathogenesis of HCC remains to be clarified, although some related factors have been reported, such as genetic and epigenetic alterations, inflammation, dysregulation of cell signaling pathways, viral factors, and metabolic changes. Therefore, it is necessary to explore the novel mechanism of HCC in order to provide important value for clinical treatment.

The relationship between HCC and cuproptosis is an emerging area of research that explores how copper metabolism and the cuproptosis may influence the development and progression of HCC. Copper is a double-edged sword for tumor cells: the cancer-promoting mechanism of copper is mainly copper-dependent cell proliferation and angiogenesis, and the cancer-inhibiting effect of copper is mainly realized through cuproptosis [30]. During the past three years, many bioinformatic analyses have found that cuproptosis-related genes (CRGs) are associated with HCC progression, prognosis, immune infiltration, and therapeutic responses [31–34]. High FDX1 expression leads to the decrease in HCC cell viability and increase in cell sensitive to Cu^{2+}, and knockdown of FDX1 promotes HCC cell proliferation and migration, indicating that FDX1 is correlated with cuproptosis in HCC [35]. HCC in advanced stage shows more lower expression of FDX1, indicating that FDX1 may be associated with HCC progression [36]. Mechanistically, mitochondrial protein FDX1 deficiency leads to metabolic reprogramming and oxidative stress, which activates PINK1/Parkin-mediated mitophagy and PI3K/AKT pathway to facilitate HCC proliferation, invasion and metastasis. Thus, FDX1 is a tumor suppressor in HCC [36]. In addition, DLAT and GLS have also been shown to promote the migration and proliferation of HCC cells [37,38]. Thus, cuproptosis is intimately related to the occurrence

Table 1
Expression patterns of cuproptosis-related genes in diverse liver diseases and their clinical implication.

Disease	Cuproptosis-related gene (Upregulated or downregulated)	Relevance to disease
Hepatocellular carcinoma, HCC [32,36,44–47]	ATP7A, SLC25A3, SCO2, COA6, TMEM199, ATP6AP1, LIPT1, DLAT, PDHA1, MTF1, ACP1, FDX2, NUBP2, CIAPIN1, ISCA2 , NDOR1, PDXK, UBE2D2 ↑ AOC1, FDX1, MT-CO1 , ACO1, SLC31A1, ↓	The expression changes of these genes are associated with the prognosis and tumor microenvironment of HCC. Upregulated PDXK can promote the proliferation and metastasis of HCC. Additionally, genes like ATP7A and LIPT1 are implicated in copper metabolism and their dysregulation may influence the progression of HCC. Downregulation of FDX1 and ACO1 has been linked to poorer prognosis, potentially impacting mitochondrial function and oxidative stress responses. DLAT expression increases with the clinical stages of HCC, and furthermore, high DLAT expression is significantly associated with tumor size. SLC31A1 expression is closely associated with overall survival and disease-free survival in HCC. UBE2D2 exhibits prognostic significance in HCC. FDX1 downregulation promotes HCC cell proliferation, invasion in vitro and growth, metastasis in vivo.
Wilson disease (WD) [27]	ATP7B mutation	ATP7B gene mutations prevent copper from being excreted via bile, causing copper to accumulate abnormally in the liver and other organs, leading to Cuproptosis.
Metabolic-associated fatty liver disease (MAFLD) [48,49]	DLD, PDHB ↑	Elevated DLD and PDHB expression affects acetyl-CoA, pyruvate metabolism and tricarboxylic acid cycle.
Acetaminophen (APAP)-induced liver injury [50]	NLRP3, POLD1,GLS ↑ FDX1,PDHB,MTF1,PPAT,ACO2,DLST,NFE2L2,DLD,PDHA1 ↓	These genes are significantly associated with aerobic respiration, mitochondrial respiratory chain, citrate cycle, and pyruvate metabolism.
Hepatic ischemia-reperfusion injury [51,52]	DLAT, NFE2L2, NLRP3, PLAT, GNL3, ALAS1 ↑ ATP7B, DBT, DLD, DPYD, ISCA2, LIAS, LIPA, PDHB ↓	NLRP3, ATP7B, and NFE2L2 are potential biomarkers for predicting HIRI.

and progression of HCC. On the other hand, GLS has been identified as a novel diagnostic and prognostic biomarker for HCC [38]. Diminished FDX1 expression has been associated with poor prognosis in HCC patients [35,39]. The expression of DLAT is also associated with tumor prognosis, and a higher risk associated with DLAT is indicative of worse OS and clinicopathological characteristics [40]. Moreover, cuproptosis affects the immune microenvironment and cell-cell communication in HCC. HCC patients with different cuproptosis subtypes exhibit different immune cell infiltration features. Greater immune and stromal cell infiltration are observed in the high-risk group and are associated with unfavorable prognosis [31,34]. Furthermore, cuproptosis manifests closely association with the immunotherapy of HCC patients. Cuproptosis-related risk signature can correlate individual cuproptosis subtypes with the patient's sensitivity to immunotherapy, suggesting the potential usefulness of the signature for personalized therapy. The accuracy of the cuproptosis-related risk signature for predicting the response to immunotherapy has been confirmed by analysis in the IMvigor210 cohort [34]. Table 1 summarized the expression patterns of cuproptosis-related genes and their clinical implication.

Of note, some studies have linked cuproptosis with ferroptosis. The combination of ES-Cu and sorafenib, a ferroptosis inducer, significantly inhibits the growth of liver tumor cells compared with administration alone in a xenotransplantation model of nude mice. Mechanistically, ferroptosis inducers inhibit the degradation of FDX1 protein mediated by mitochondrial matrix-associated proteases, which increases protein lipoylation levels and inhibits intracellular glutathione (GSH) synthesis by suppressing cystine intake, thus aggravating cuproptosis [41]. This finding suggests that there may be complex interactions between cuproptosis and other cell death modes, which may have a significant impact on the development and treatment of liver cancer.

In addition, some therapeutic strategies targeting cuproptosis have been explored. For example, taxifolin has been reported to inhibit HCC progression by inducing cuproptosis via an SLC31A1-mediated pathway [42]. Furthermore, studies have identified potential chemotherapeutic candidates such as LIPT1-zebularine, DLAT-valdecoxib, GLS-dasatinib, and CDKN2A-tozasertib, which exhibit strong binding affinity with cuproptosis-related genes, highlighting their potential for targeted therapy in HCC [43].

Collectively, although the existing studies have not proven the definitive link between cuproptosis and liver cancer, targeting cuproptosis has shown the potential for the treatment of liver cancer. Understanding the mechanism of cuproptosis in-depth and exploring the combination of cuproptosis and other therapeutic methods may provide new ideas for the treatment of liver cancer.

3.2. Cuproptosis and Wilson disease

Wilson disease (WD), also known as hepatolenticular degeneration, is an autosomal recessive disorder characterized by the excessive accumulation of copper in the body, particularly in the liver, brain, and other tissues [53]. The mutation in ATP7B gene, which is responsible for the transport and excretion of copper, affects the effective elimination of excess copper, leading to toxic levels that can cause significant damage to various organs [54]. The hepatic manifestations of WD patients includes fatigue, abdominal pain, jaundice, liver enlargement, and liver failure [55].

As a hallmark feature of Wilson disease, copper concentration is remarkably elevated in the livers of WD patients, higher than 55 μg/g tissue dry weight, even exceeding 250 μg/g tissue dry weight in some patients [56]. Excessive copper in hepatocytes induces the aggregation of lipoylated DLAT, which is associated with impairment of mitochondrial TCA cycle, resulting in proteotoxic stress and ensuing cuproptosis [57]. Cuproptosis has been proved in mouse models of Wilson disease, suggesting the probability that cuproptosis promotes the development of Wilson disease in patients. The exacerbation of cuproptosis in liver cells of WD patients may aggravate liver damage, accelerate the development of liver fibrosis, cirrhosis and other sequelas. For patients with Wilson disease, it is crucial to control copper metabolism disorder and copper toxicity in time and effectively. Drugs used to treat Wilson disease

typically include copper chelators such as D-Penicillamine and trientine, as well as decoppering agents [58–60], which lower serum concentrations of copper ion and reduce the risk of copper toxicity. One of the purposes of these therapeutic measures may be to protect the liver and other organs from cuproptosis. Therefore, cuproptosis is closely linked to the pathogenesis of Wilson disease and has a significant impact on the treatment and prognosis of WD patients. Strengthening the study on cuproptosis provides profound insights into the pathophysiology of Wilson disease, and offers new perspectives and targets for the treatment of WD.

3.3. Cuproptosis and metabolic-associated fatty liver disease (MAFLD)

Metabolic-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is defined by the presence of hepatic steatosis (fat accumulation in liver cells) in individuals with metabolic risk factors such as obesity, insulin resistance, and type 2 diabetes. The development of MAFLD is multifactorial, involving a combination of genetic, environmental, and lifestyle factors. MAFLD is emerging as the most common liver diseases worldwide, affecting a substantial proportion of individuals, particularly in developed countries where obesity and sedentary lifestyles are prevalent [61]. It represents a significant public health challenge due to its high prevalence, potential for serious liver-related complications, and association with other metabolic disorders [62].

The pathogenesis of MAFLD involves a multifactorial interplay, including insulin resistance, inflammation, oxidative stress, mitochondrial dysfunction, and gut microbiota. Recent studies, especially bioinformatics analysis, provide hints for the relationship between cuproptosis and MAFLD. Serum copper levels are positively correlated with body mass index (BMI), leptin, and insulin resistance [63], which are all risk factors for MAFLD. Bioinformatics analysis showed that some cuproptosis genes (ATP7B, SLC31A1, LIAS, DLD, DLAT, PDHA1, PDHB, MTF1, NFE2L2, DBT) are significantly differentially expressed in MAFLD patients compared with healthy subjects, suggesting that these cuproptosis-related genes play an important role in the development of MAFLD [64,65]. Moreover, the clusters with a higher cuproptosis degree have a greater degree of hepatocyte balloon-like transformation and a higher score of MAFLD activity, further indicating the close relationship between cuproptosis and NAFLD [64]. Mechanistically, excess serum copper activates metal regulatory transcription factor 1 (MTF-1), inhibits the specificity protein 1 (SP1)/Fyn pathway [66], and up-regulates lipid metabolism and lipogenesis, therefore inducing the occurrence of MAFLD [67,68]. In addition, the subgroups in which DLD and DLAT are located not only have a higher degree of cuproptosis, but also have differences in immune infiltration and more inflammatory activities, indicating that cuproptosis accelerates the progression of MAFLD and aggravates the immune response [64]. Moreover, elevated DLD and PDHB expression affects acetyl-CoA, pyruvate metabolism and tricarboxylic acid cycle, thus exacerbating copper toxicity [49]. Using a MAFLD mouse model, DLD and PDHB were documented to exacerbate hepatic steatosis and induce liver inflammation through cuproptosis [67]. Importantly, cuproptosis-related DEGs exhibit good diagnostic and predictive value for MAFLD [64,65]. Overall, cuproptosis may be associated with the occurrence, progression, diagnosis, and prognosis prediction of MAFLD. More basic studies, larger sample size, and more detailed clinical studies are needed to further explore and clarify the correlation between cuproptosis and MAFLD.

3.4. Cuproptosis and hepatic ischemia-reperfusion injury

Hepatic ischemia-reperfusion injury (HIRI) represents a significant complication observed in diverse clinical scenarios, including liver resection, liver transplantation, and trauma. It involves a biphasic pathophysiological progression: initial ischemia-induced injury and subsequent reperfusion injury [51]. Multiple clinical studies and basic research reveal that the occurrence of HIRI is related to a series of complex events, such as hypoxic injury, intracellular metabolic dysfunction, excessive oxidative stress, innate and adaptive immune responses, and abnormal cell death [69–71].

Ischemia and reperfusion-induced hepatocyte death is characterized by various distinct, often complementary or overlapping, regulated form of cell death, including apoptosis, autophagy, necroptosis, ferroptosis, and pyroptosis. Cuproptosis, a newly identified form of cell death, has been implicated to play crucial roles in heart or brain ischemia-reperfusion damages [72–74]. Most recently, some studies have also hinted at an underlying connection between cuproptosis and HIRI. The authors examined the differential expression of cuproptosis-related genes (CRGs) in both HIRI and control liver samples obtained from GEO database, and identified dozens of DE-CRGs. Of which, DLAT, NFE2L2, NLRP3, PLAT, GNL3, ALAS1, TSC22D2, KLF5, GTF2B, DNTTIP2, SLFN11, HNRNPU, and PPAT are upregulated, while ATP7B, DBT, DLD, DPYD, ISCA2, LIAS, LIPA, and PDHB are downregulated [51,52]. NLRP3, ATP7B, and NFE2L2 have been identified as reliable and robust biomarkers for predicting HIRI [51]. Future studies are expected to further elucidate the specific mechanisms of cuproptosis in hepatic ischemia-reperfusion injury and provide novel therapeutic targets for its modulation. Such advancements could open up new therapeutic avenues for liver protection and the management of HIRI.

3.5. Cuproptosis and drug-induced liver injury

Drug-induced liver injury (DILI) is a type of liver disorder caused by the direct or indirect toxic effects of drugs and their metabolites on hepatocytes [75]. DILI has emerged as a significant global public health challenge. Especially, acetaminophen (APAP)-induced liver injury (AILI) has drawn widespread attention due to its high prevalence and severe clinical consequences [76]. APAP overdose leads to a substantial increase in the production of N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite [77]. Excessive NAPQI triggers glutathione (GSH) depletion, mitochondrial oxidative stress, dysfunction, and eventually hepatocyte death [78–80].

Based on the overwhelming experimental and clinical evidence, diverse forms of PCDs such as apoptosis, necroptosis, pyroptosis and ferroptosis have been documented to promote APAP-induced cell death [81–84]. So far, no experimental work has investigated the potential role of cuproptosis in drug-induced liver injury. Of note, mitochondrial oxidative stress and dysfunction as well as GSH exhaustion are the major cellular events involved in both AILI and cuproptosis [50]. This finding indicates the relationship between cuproptosis and the development and progression of AILI. Bioinformatics analysis showed that 24 CRGs are differentially expressed between APAP and control samples. These DE-CRGs can be enriched in lipoic acid metabolism, the TCA cycle, iron-sulfur cluster binding, and so on. Moreover, four genes SDHB, PDHA1, NDUFB2, and NDUFB6 have been identified as potential diagnostic biomarkers for AILI [50]. On the other hand, the experimental results suggest a potential involvement of cuproptosis in AILI. Although the precise molecular mechanisms underlying the role of cuproptosis in DILI remain to be fully elucidated, current findings provide an innovative framework for understanding the pathogenesis of drug-induced liver injury. Additionally, they open up new possibilities for therapeutic interventions by targeting copper metabolism.

3.6. Cuproptosis and liver fibrosis

When stimulated by some factors such as alcohol, drugs or cholestasis, hepatic stellate cells (HSCs) are activated to promote the production of extracellular matrix (i.e., collagen, glycoproteins, and proteoglycans). The diffuse deposition and abnormal distribution of these ECMs contribute to liver fibrosis [85,86], a pathological reparative response of the liver to chronic injury [87]. Liver fibrosis is considered a critical step in the progression of various chronic liver diseases (CLDs) to cirrhosis.

The initiation, development and resolution of hepatic fibrosis are influenced by various cytokines, chemokines, damage-associated molecular patterns (DAMPs) and signaling pathways. Especially, programmed cell death (PCD) plays a pivotal role in maintaining homeostasis. A significant number of studies in recent years have indicated that the progression of hepatic fibrosis is intimately linked to PCD processes such as apoptosis, autophagy, pyroptosis, and necroptosis [88]. Most recently, the substantial contribution of transition metals, particularly copper ions, to the development of fibrotic diseases, has been brought to light [89]. Dysregulation of copper metabolism is strongly linked to the development of hepatic fibrosis [89]. Patients with cirrhosis and liver fibrosis have significantly higher levels of serum copper ion compared to healthy individuals [90]. In addition, the development of liver fibrosis is accelerated by copper accumulation. Mechanistically, hepatocyte damage triggered by cuproptosis may activate inflammatory responses in the liver, and promote the release of inflammatory mediators. These mediators can stimulate HSC activation, leading to collagen deposition and subsequent fibrosis. Remarkably, HSC cuproptosis can promote the resolution of liver fibrosis. In-depth exploration of the cuproptosis pathway will help uncover the pathogenesis of liver fibrosis. Targeting copper metabolism and cuproptosis may serve as a viable therapeutic strategy for the treatment of liver fibrosis. In this regard, some pharmacological agents have been demonstrated to have the potential in reducing hepatic fibrosis through the modulation of copper homeostasis [89].

4. Conclusions and future perspectives

Cu is an essential trace element in the human body. Cuproptosis is a newly discovered mode of cell death in which excess copper interferes with the TCA cycle in mitochondria, thereby triggering cell death. This discovery marked a significant milestone in the understanding of regulated cell death, highlighting the role of copper accumulation in inducing cell death through unique mechanisms.

At present, the study on cuproptosis is still in its infancy. There are a relatively large number of studies investigating the relationship between cuproptosis and liver cancer. Although cuproptosis has exhibited the potential in cancer treatment, the clinical performance of ES-Cu, which is highly expected, is not ideal. WD, as a disease caused by copper accumulation, may be inextricably related to cuproptosis, however, this connection needs to be verified by experimental research. The pathogenesis of MAFLD has not yet been elucidated, and the discovery of cuproptosis may provide a new idea. In-depth exploration of the unique role of cuproptosis in MAFLD is of great significance to elucidate the occurrence and development mechanism of MAFLD, and can also provide new therapeutic targets (such as DLD and PDHB) and new ideas for clinical treatment of MAFLD. The study on the relationship between cuproptosis and viral liver disease is also imminent, considering that China is a main epidemic area of hepatitis B.

The future research on cuproptosis mechanism can focus on the association between cuproptosis and other cell death modes, so as to discover the intrinsic relationship between different cell death modes and promote the progress of cell death research. Moreover, we hope to find a new gold standard for classifying and staging liver-related diseases by analyzing the expression of CRGs, and develop personalized treatment plans according to the disease characteristics and copper metabolism status of different patients, so as to improve treatment effectiveness and survival rate of patients. Combining copper ionophores with emerging treatment methods such as nanotechnology is also worth further exploration. Furthermore, a thorough understanding of the role of cuproptosis in liver diseases will provide new targets and strategies for early diagnosis, disease prevention, and treatment.

In summary, the discovery of cuproptosis opens up new avenues for exploring the implications of copper dysregulation in various diseases and the potential for developing targeted therapies that exploit the cuproptosis pathway. Researchers are investigating how the pathways involved in cuproptosis can be targeted to develop novel therapeutic strategies for diseases associated with copper metabolism. Ongoing studies will continue to deepen our understanding of this novel form of cell death and its applications in medicine, which is expected to bring better treatment outcomes and improve the quality of life of patients.

Author contributions

QY, XL, and HT prepared the original manuscript and data; YC and LB revised and finalized the manuscript. All authors have read and approved the final draft of the paper.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Data availability

No datasets were generated or analysed during the current study.

Conflict of interest

The authors declare no competing interests.

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